The Claimed Invention

The claims are drawn to a method of treatment requiring at least two elements not shown in the prior art:

(a) treatment of **individuals in need of alteration of the production of reproductive hormones for treatment of disorders in which the levels of reproductive hormones are involved** and

(b) by **specifically** alterating SR-BI expression or binding, either by administration of a compound which inhibits SR-BI as defined on page 11 of the application or which selectively increases expression of SR-BI.

The claim language excludes the general treatment using estrogen (see page 11, lines 2-9). While it has been observed that estrogen affects cholesterol blood levels, this alone does not make obvious that there is any affect on SR-BI. It was only after applicant specifically observed the effect of knocking out SR-BI expression in animals on their reproductive abilities, that one could draw the corollary that this made for a way to treat disorders associated with reproductive hormone levels.

The claim language also excludes merely administering an agent to animal cells or tissues and observing an effect on SR-BI.

Inherency is applicable only when the prior art destroys novelty - i.e., is prior art under section 102, and discloses each claimed element, either implicitly or explicitly. To be a novelty destroying reference, the reference must disclose administration of an agent which specifically alters SR-BI expression or binding to an animal or person in need of treatment for a disorder involving the reproductive hormones.

Estrogen does not specifically alter SR-BI expression or binding. It is well known that it does not specifically alter SR-BI expression or binding since it is involved in the treatment of a wide variety of disorders, ranging from birth control to osteoporosis. The Examiner has provided no evidence otherwise, and in fact has provided evidence of the generalized mechanisms of action with the art that has been cited. Additional evidence demonstrating that the action of the compounds described in the prior art is not selective for SR-BI is enclosed.

None of the prior art discloses treatment of a human or animal with a disorder involving reproductive hormones.

To more clearly distinguish the prior art, the claims have been amended to recite that the compound either selectively increases expression of SR-BI or is a "direct inhibitor" which is defined on page 11 at lines 11-17. These include nucleotide molecules which bind to the SR-BI gene, small organic molecules which bind to the SR-BI protein, soluble SR-BI protein or fragments thereof, and compounds such as antibodies and fragments thereof which block binding of HDL to SR-BI.

Rigotti, et al.

Rigotti, et al., teach that SR-BI mediates transfer of cholesteryl esters and that it therefore plays a role in the selective uptake of lipids by cells. Rigotti also reports that SR-BI is expressed in elevated amounts in the liver, the adrenal gland, and the ovary, but notes "measurement of the absolute levels and changes in SR-BI mRNA levels may not necessarily reflect the levels of SR-BI protein and SR-BI activity in tissues or cells. Rigotti, et al. further reports that administration of estrogen to rats, administration of human chorionic gonadotropin to male rats, and administration of dexamethasone to rats increased expression of SR-BI in Leydig cells and

adrenocortical cells, respectively. None of estrogen, human chorionic gonadotrophin, or dexamethasone selectively increase SR-BI but have a wide variety of other activities. None were administered to an animal with a disorder involving reproductive hormones. All that was shown was that the expression of SR-BI was increased in Leydig cells or adrenocortical cells. Rigotti, et al., do not even speculate that selective modification of SR-BI expression or binding could play a role in treatment of disorders involving reproductive hormones, referring only to the potential role in atherogenesis and lipid metabolism.

In summary, Rigotti, et al., fails to disclose the claimed method, explicitly or inherently.

Spona, et al.

Spona is a report on administration of a birth control agent containing levonorgestrel in combination with ethinylestradiol to females. This does not describe administration of an agent which selectively alters SR-BI expression or binding, but is another example of administration of steroidal compounds having a variety of different actions.

Bajetta, et al.

Bajetta, et al. describes administration of a selective inhibitor of estrogen synthesis, formestane, by inhibiting aromatase enzymes. This clearly is distinct from a compound which is used to selectively alter SR-BI expression or binding.

Cirkel

Cirkel reviews treatment of endometriosis using the combination of progestogens, danazol and luteinizing hormone-releasing hormone (LHRH) agonists. As noted at page 93, "danazol thereapy is accompanied by many general, metabolic, hypo-oestrogenic and hyperandrogenic side effects". As noted on page 95, LHRH causes a significant decrease in both

pituitary hormones.

Whitcroft and Stevenson

Whitcroft and Stevenson describe the treatment of females with hormone replacement, and its effects on a variety of different conditions, including cardiovascular disease and osteoporosis. Whitcroft and Stevenson clearly establish that treatment with reproductive hormones involves many different mechanisms of actions, and is definitely not something that "selectively alters SR-BI expression or binding".

In summary, none of the art discloses the claimed elements and therefore fails to destroy the novelty of the claims. Since there is no recognition in the prior art that SR-BI plays a role in disorders associated with reproductive hormones, there can be no motivation to modify and combine the teachings of the references to achieve the claimed method.

Rejections under 35 U.S.C. §112

Claims 1-16 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification failed to support the breadth of the claims. This rejection is respectfully traversed.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g.*, Genentech, Inc. v. Novo Nordisk A/S, 108 F3d at 165, 42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also In re Fisher, 427 F.2d at 839, 166 USPQ at 24; United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343 (CCPA 1976)). The fact that

experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (M.I.T. v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985)).

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

> The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.
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> *Id.* at § 2164.05 (emphasis added).

In this case, the examiner has consistently relied on conclusory statements without putting forth specific reasons describing why the claims are not enabled by the specification. The patent examiner cannot just assert that the application is not enabled. As stated in In re Marzocchi at 439 F.2d 220 (CCPA 1971:

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made [, enablement under § 112, first paragraph], to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224.

The MPEP instructs examiners to make specific findings of *facts* to rebut Appellants' presumption and "specifically identify what information is missing and why one of skill in the art could not supply the information without undue experimentation." MPEP at § 2164.05. The examiner should provide references to support a *prima facie* case of lack of enablement. *Id.*

Lastly, there is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing* Gould v. Quigg, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.*

The Specification is Enabling

The examiner's position that unless there is a working example in the specification, the claims are not enabled, is clearly contrary to the legal standard articulated above. The examiner has rejected the claims as enabled only based on the actual working examples (example 3 and 8, which represent widely different chemical compounds), ignoring the rest of the specification. However, there is no requirement for any working examples - and in this case, applicants have provided two examples and a great deal of guidance as to the other types of compounds that can be used. The statement that there is "no guidance" of the use of antisense oligonucleotides...small organic molecules or soluble SR-BI proteins..." ignores the specification in its entirety!

The examiner's attention is drawn to the specification:

Nucleic acid regulators (including antisense, ribozymes, etc): page 18, line 8 to page page 19, line 9; page 20, line 21 - page 24, line 3

Small molecule design: page 19, line 10 - page page 20, line 20

Receptor Protein Fragments: page 24, line 4 - page 25, line 30

Methods for screening for drugs or other useful compounds: page 14, line 8 - page 17, line 13; page 18, lines 1 - 21

Examples:

Examples 1 and 5, overexpression of SR-BI in transgenic cells using adenoviral vector to transform cells with SR-BI cDNA

Examples 2 and 4, increased expression of SR-BI in tissues treated with estrogen

Example 3, showing upregulation of SR-BI by estrogen and down-regulation of SR-BI by upregulation of the LDL receptor

Examples 6 and 7: generation of SR-BI knockout animals

Example 8: inhibition of SR-BI with SR-BI antibody

The examiner has also failed to comply with the requirements that the conclusory statements be supported by more than the examiner's position. Instead, we have only an opinion which is simply based on an inaccurate conclusion regarding the teachings of the specification, and supported by no extraneous evidence.

The rejection should therefore be withdrawn.

Allowance of claims 1-16 is therefore earnestly solicited. All claims as pending upon entry of this amendment are attached in an appendix for the convenience of the examiner.

Respectfully submitted,

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